IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
WACO DIVISION

Ravgen, Inc., Plaintiff, v. Natera, Inc. and NSTX, Inc., Defendants.	Civil Action No. 6:20-cv-451 **JURY TRIAL DEMANDED**

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Ravgen, Inc. ("Ravgen"), for its Complaint against Defendants Natera, Inc. and NSTX, Inc. (collectively "Defendants"), hereby alleges as follows:

NATURE OF THE ACTION

1. This is a civil action for infringement of United States Patent Nos. 7,727,720 (the "'720 Patent") and 7,332,277 (the "'277 Patent") (collectively the "Patents-in-Suit"), arising under the Patent Laws of the United States, 35 U.S.C. §§ 271, *et seq*.

THE PARTIES

2. Plaintiff Ravgen is a Delaware corporation with its principal place of business at 9241 Rumsey Rd., Columbia, MD 21045. Ravgen is a pioneering diagnostics company that focuses on non-invasive prenatal testing. Ravgen has spent millions of dollars researching and developing novel methods for the detection of cell-free DNA to replace conventional, invasive procedures. Ravgen's innovative cell-free DNA technology has various applications, including non-invasive prenatal and other genetic testing. Those efforts have resulted in the issuance of several patents, including the Patents-in-Suit.

3. Defendant Natera, Inc. is a Delaware corporation with its principal place of business at 201 Industrial Road, San Carlos, California 94070. (Ex. 9 at 1 (Texas Secretary of State report for Natera, Inc.).) Natera, Inc. is registered to do business in the state of Texas. (*Id*.) Natera, Inc. has appointed National Registered Agents, Inc., 1999 Bryan St., Ste. 900 Dallas, TX 75201 as its agent for service of process. (*Id*.) Natera, Inc. maintains diagnostic testing facilities, laboratories, and office space for supporting and processing diagnostic tests at 13011 McCallen Pass, Building A, Suite 100 Austin, TX 78753 and 106 East Sixth Street, Suite 934, Austin, TX (Clinical Laboratory Improvement Amendments of 1988 ("CLIA") ID number 45D2093704). (*See* Ex. 11 at 1 (https://www.builtinaustin.com/company/natera); Ex. 12 at 3 (https://www.natera.com/hrzn27c).)

4. Defendant NSTX, Inc. is a Delaware corporation with its principal place of business at 13011 McCallen Pass, Building A, Austin, TX 78753. (*See* Ex. 13 at 282 (Natera, Inc. Form 10-Q Filing (November 9, 2017), Ex. 10.2, http://investor.natera.com/static-files/92b40103-3740-41ec-bbe2-bd319fbed285) at 341 (listing "13011 McCallen Pass, Build. A, Suite 100 Austin, TX 78753" as the address for NSTX, Inc.).) NSTX, Inc. is registered to do business in the state of Texas. (Ex. 10 at 1 (Texas Secretary of State report for NSTX, Inc.).) NSTX, Inc. has appointed National Registered Agents, Inc., 1999 Bryan St., Ste. 900 Dallas, TX 75201 as its agent for service of process. (*Id*.) NSTX, Inc. is a wholly-owned subsidiary of Natera, Inc. (*See, e.g.*, Ex. 13 at 177 (listing under "Schedule 6.8 Existing Subsidiaries" "NSTX, Inc." with "Natera, Inc." as the "Direct & indirect owner(s)").)

5. Defendants commercialize genetic tests using cell-free DNA, including: a non-invasive prenatal diagnostic test for the determination of fetal chromosomal abnormalities marketed under the tradename "Panorama"; a non-invasive prenatal diagnostic test to screen

single-gene disorders marketed under the tradename "Vistara"; a circulating tumor DNA (ctDNA) test for Minimal Residual Disease (MRD) assessment and surveillance marketed under the tradename "Signatera"; and, a donor-derived cell-free DNA (dd-cfDNA) test for assessing the risk of allograft rejection marketed under the tradename "Prospera." Defendants offer and market those tests throughout the United States, at least through the website, www.natera.com. (*See generally* Ex. 14 (https://www.natera.com/womens-health/panorama-nipt-prenatal-screening); Ex. 15 (https://www.natera.com/womens-health/vistara-nipt-single-gene-test); Ex. 16 (https://www.natera.com/oncology/signatera-advanced-cancer-detection); Ex. 17 (https://www.natera.com/organ-transplantation/prospera-organ-transplantation-assessment.).)

JURISDICTION AND VENUE

6. Ravgen incorporates by reference paragraphs 1–5.

7. This action arises under the patent laws of the United States, including 35 U.S.C. §§ 271, *et seq*. The jurisdiction of this Court over the subject matter of this action is proper under 28 U.S.C. §§ 1331 and 1338(a).

8. Venue is proper in this District pursuant to U.S.C. §§ 1391(b), (c), (d) and 1400(b) because Defendants have a permanent and continuous presence in, have committed acts of infringement in, and maintain regular and established places of businesses in this District.

9. By registering to conduct business in Texas and by having facilities where they regularly conduct business in this District, Defendants have a permanent and continuous presence and regular and established places of business in the Western District of Texas.

10. Natera, Inc. maintains regular and established places of businesses in this District, including at least its diagnostic testing facilities, laboratories, and office space for supporting and processing diagnostic tests at 13011 McCallen Pass, Building A, Suite 100, Austin, TX 78753 and

106 East Sixth Street, Suite 934, Austin, TX (CLIA ID number 45D2093704). (*See* Ex. 11 at 1; Ex. 12 at 3.)

11. NSTX, Inc. maintains regular and established places of businesses in this District, including at least its CLIA-compliant diagnostic testing facilities, laboratories, and office space at 13011 McCallen Pass, Building A, Suite 110, Austin, TX 78753. (*See* Ex. 18 at 25 (Natera, Inc. Form 10-K Filling (Filed March 2, 2020), http://investor.natera.com/static-files/97e03872-d617-4ba8-b7ea-18a52f368eae) ("In September 2015, the Company's subsidiary entered into a long-term lease agreement for laboratory and office space totaling approximately 94,000 square feet in Austin, Texas.").) For example, NSTX, Inc. has a CLIA Certificate for its Austin facilities, as shown on the Centers for Medicare & Medicaid Services (CMS) and Centers for Disease Control and Prevention (CDC) websites:

Certificate / Application Type	Name and Address / CLIA Number	Telephone #	Certificate Expiration Date	Lab Testing Performed In
Compliance	NSTX, INC 13101 MCCALLEN PASS, BUILDING A, SUITE 110 AUSTIN, TX 78753 #45D2093704	(650) 249-9090	12/1/2020	Independent

(Ex. 19 at 1 (https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/CLIA_Laboratory_Demographic_Information) (showing search result for CLIA number "45D2093704").)

CLIA Number	Laboratory Type	Certificate Type	Laboratory Name & Address
45D2093704	Independent	Compliance	Nstx, Inc 13101 Mccallen Pass, Building A, Suite 110, Austin, TX 78753 Tel: (650) 249-9090

(Ex. 20 at 1 (https://www.cdc.gov/clia/LabSearch.html) (showing search result for CLIA number "45D2093704").)

12. The testing facilities, laboratories, and office space at 13011 McCallen Pass, Austin, TX 78753 identify both NSTX, Inc. and Natera, Inc. as occupants:

13. Defendants have numerous employees in this judicial District with responsibilities relating to the accused genetic testing products, including the Panorama, Vistara, Signatera, and

Prospera tests. For example, Natera, Inc. has over 20 job openings listed for its Austin, TX location(s), including "Medical Laboratory Scientist I" under the heading "NIPT Panorama (NIPT)," "Associate Laboratory Director," "Technical Product Manager R&D - Oncology LIMS," and "Laboratory Operations Manager." (*See generally* Ex. 21 (https://www.natera.com/careers/job-openings).) The "Associate Laboratory Director" position's "Primary Responsibilities" include:

> Review, approve, and sign-out reports for a variety of clinical molecular/**cytogenetic and/or oncologic results**, **including NIPT**, carrier screening, PGD/PGS, products of conception and **oncology testing** on platforms including SNP array analysis, NGS, and other methodologies. . .
>
> Provide clinical and technical support for genetic counselors and other laboratory personnel.

(Ex. 22 at 1 (https://www.natera.com/careers/job-openings?gnk=job&gni=8a78879e67ebaa7a016811bdc9a84f86&lang=en) (emphasis added).) The position "Technical Product Manager R&D - Oncology LIMS" is described as supporting the Signatera product. (Ex. 23 at 1 (https://www.natera.com/careers/job-openings?gnk=job&gni=8a78839f7184b92601718aa644fb6b8c&lang=en) (job listing for "Technical Product Manager R&D - Oncology LIMS" in "Austin, TX," stating "For this position focused on Oncology LIMS [laboratory information management system], you will be working on projects and maintenance for LIMS related to our Signatera cancer detection product.").) Additionally, Natera, Inc. previously listed a job opening for its Austin location to support its Prospera product. (Ex. 24 at 1 (https://www.linkedin.com/jobs/view/prospera-clinical-operations-coordinator-at-natera-1450349453/) (previous job listing for "Prospera Clinical Operations Coordinator" in Austin, Texas).)

14. Defendants offer for sale and sell cell-free DNA tests that employ methods claimed in the Patents-in-Suit, including the Panorama, Vistara, Signatera, and Prospera tests, throughout the United States, including through their website, which is accessible in this District.

15. Natera, Inc. has committed acts of direct infringement in this judicial District itself and/or through its wholly owned subsidiary NSTX, Inc. For example, on information and belief, Natera, Inc., itself and/or through its wholly owned subsidiary NSTX, Inc., which acts as an agent and alter ego of Natera, Inc. and is completely controlled and dominated by Natera, Inc., performs infringing methods in this District by using the Panorama tests, including processing the results of those tests, in offices and laboratories at 13011 McCallen Pass, Building A, Austin, TX 78753.

16. NSTX, Inc. has committed acts of direct infringement in this judicial District. For example, on information and belief, NSTX, Inc. performs infringing methods in this District by using the Panorama tests, including processing the results of those tests, in offices and laboratories at 13011 McCallen Pass, Building A, Austin, TX 78753.

17. Venue is also proper because NSTX, Inc. is a wholly-owned subsidiary of Natera, Inc., operates as an agent and alter-ego of Natera, Inc., and is completely controlled and dominated by Natera, Inc. Natera, Inc. directs and is involved in the activities of NSTX, Inc., and they operate as a single company. As the corporate parent of NSTX, Inc., Natera, Inc. has participated in the commission of patent infringement in this judicial District, including by making, using, offering for sale, and/or selling the Panorama, Vistara, Signatera, and Prospera tests in this District and elsewhere that led to foreseeable harm and injury to Ravgen. The officers of NSTX, Inc. are also officers of Natera, Inc. For example, Matthew Rabinowitz, the current Executive Chairman of the board of directors of Natera, Inc., was the former CEO of both Natera, Inc. and NSTX, Inc. and was a signatory to an August 8, 2017 Pledge and Security Agreement on behalf of both Natera,

Inc. and NSTX, Inc. (*See* Ex. 13 at 307.) Michael Brophy, Natera, Inc.'s Chief Financial Officer, has also served concurrently as the Chief Financial Officer of NSTX, Inc. and was a signatory to a September 12, 2019 Amendment to the August 8, 2017 Pledge and Security Agreement on behalf of both Natera, Inc. and NSTX, Inc. (Ex. 25 at 108 (http://investor.natera.com/static-files/3b4e548b-a257-4d4d-9491-15f674b9b63c, Natera, Inc. Form 10-Q Filing (Filed at November 8, 2019), Ex. 10.1).) Jonathan Sheena, Natera, Inc.'s Chief Technology Officer, also serves as NSXT, Inc.'s Chief Technology Officer according to NSTX, Inc.'s filing with the Texas Secretary of State. (Ex. 9 at 4; Ex. 10 at 4.) All of the individuals listed as Directors of NSTX, Inc. in NSTX, Inc.'s filing with the Texas Secretary of State also appear as Directors of Natera, Inc. in Natera, Inc.'s filing with the Texas Secretary of State, including Roelof F. Botha, Todd Cozzens, Edward C. Driscoll, Jr., James I. Healy, John Steuart, Gail Marcus, and Herm Rosenman. (Ex. 9 at 4; Ex. 10 at 4.)

18. Natera, Inc. is subject to this Court's jurisdiction pursuant to due process and/or the Texas Long Arm Statute due at least to its substantial business in this State and judicial District, including at least regularly doing and soliciting business at its Austin facilities, and engaging in persistent conduct and/or deriving substantial revenue from goods and services provided to customers in the State of Texas, including in the Western District of Texas. For example, Natera, Inc. conducts business in the District, by at least offering for sale and selling products and services that practice the claimed inventions of the Patents-in-Suit, including the Panorama, Vistara, Signatera, and Prospera tests, including through its websites, which are accessible in this District. In addition, Natera, Inc. leases and operates offices and laboratories in this District that support and process products and services that practice the claimed inventions of the Patents-in-Suit, including at least the Panorama test.

19. This Court has personal jurisdiction over Natera, Inc. due, *inter alia*, to its continuous presence in, and systematic contact with, this District and its registration in Texas. Natera, Inc. has established minimum contacts within the forum such that the exercise of jurisdiction over Natera, Inc. will not offend traditional notions of fair play and substantial justice.

20. Personal jurisdiction exists over Natera, Inc. because, Natera, Inc. directly and/or through subsidiaries or intermediaries has committed and continues to commit acts of infringement in this District by, among other things, using products and/or services that infringe the Patents-in-Suit, which led to foreseeable harm and injury to Ravgen.

21. NSTX, Inc. is subject to this Court's jurisdiction pursuant to due process and/or the Texas Long Arm Statute due at least to its substantial business in this State and judicial District, including at least part of its infringing activities, regularly doing and soliciting business at its Austin facilities, and engaging in persistent conduct and/or deriving substantial revenue from goods and services provided to customers in the State of Texas, including in the Western District of Texas. For example, NSTX, Inc. conducts business in the District, by at least offering for sale and selling products and services that practice the claimed inventions of the Patents-In-Suit, including the Panorama test. In addition, NSTX, Inc. leases and operates offices and laboratories in this District that support and process products and services that practice the claimed inventions of the Patents-in-Suit, including the Panorama test.

22. This Court has personal jurisdiction over NSTX, Inc. due, *inter alia*, to its continuous presence in, and systematic contact with, this judicial District and its registration in Texas. NSTX, Inc. has established minimum contacts within the forum such that the exercise of jurisdiction over NSTX, Inc. will not offend traditional notions of fair play and substantial justice.

23. Personal jurisdiction exists over NSTX, Inc. because, NSTX, Inc. directly and/or indirectly has committed and continues to commit acts of infringement in this judicial District by, among other things, using products and/or services that infringe the Patents-in-Suit, which led to foreseeable harm and injury to Ravgen.

BACKGROUND OF THE INVENTION

24. Dr. Ravinder S. Dhallan is the founder of Ravgen, Inc. and the inventor of several patents in the field of detection of genetic disorders, including chromosomal abnormalities and mutations. Ravgen's mission is to provide state of the art genetic testing that will enrich the lives of its patients. For example, through the use of its novel techniques in non-invasive prenatal diagnostic testing, Ravgen gives patients the knowledge they need to prepare for their pregnancies and treat diseases at an early stage.

25. Prior to founding Ravgen, Dr. Dhallan was a board-certified emergency room physician, who completed his residency at Mass General (Harvard University School of Medicine). During his time at medical school and his residency, Dr. Dhallan and his wife suffered three miscarriages. At that time, the prenatal diagnostic testing procedures available included (a) non-invasive techniques with low sensitivity and specificity, and (b) tests with higher sensitivity and specificity that were highly invasive and therefore associated with a risk for loss of pregnancy. After discovering the limitations on the available techniques for prenatal testing, Dr. Dhallan made it his mission to invent an improved prenatal diagnostic exam—one that was both non-invasive and accurate. In September of 2000, Dr. Dhallan founded Ravgen (which stands for "Rapid Analysis of Variations in the GENome") to pursue that goal.

26. Prior to Ravgen's inventions, scientists had recognized the need for a genetic testing technique that used "cell-free" or "free" fetal DNA circulating in maternal blood. A technique that

relied on circulating free fetal DNA would require only a simple blood draw from the mother and would therefore be improvement over invasive diagnostic tests.

27. However, at that time, the use of free fetal DNA for detecting chromosomal abnormalities was limited by the low percentage of free fetal DNA that could be recovered from a sample of maternal blood using existing techniques. (*See, e.g.,* Ex. 26 (Lo Y.M. et al., *Quantitative analysis of fetal DNA in maternal plasma and serum: implications for noninvasive prenatal diagnosis* AM J HUM GENET. 1998; 62(4):768-775, available at https://doi.org/10.1016/S0140-6736(97)02174-0.) Dr. Dhallan recognized that a method that could increase the percentage of free fetal DNA relative to the free maternal DNA in a sample was necessary to the development of an accurate, non-invasive prenatal diagnostic test.

28. After substantial research, Dr. Dhallan conceived that including an agent that impedes cell lysis (disruption of the cell membrane) if cells are present during sample collection, shipping, handling, and processing would permit the recovery of a larger percentage of cell-free fetal DNA (relative to the cell-free maternal DNA in a sample). Dr. Dhallan hypothesized that this new approach would decrease the amount of maternal cell lysis and therefore lower the amount of cell-free maternal DNA in the sample, thereby increasing the percentage of cell-free fetal DNA. He developed a novel method for processing cell-free fetal DNA that involved the addition of an agent that impedes cell lysis—for example, a membrane stabilizer, a cross-linker, and/or a cell lysis inhibitor—to maternal blood samples coupled with careful processing protocols. With that novel method, Dr. Dhallan was able to increase the relative percentage of cell-free fetal DNA in the processed sample.

29. Dr. Dhallan understood that his breakthrough laid the foundation for the development of accurate non-invasive prenatal diagnostic tests. For example, he published a paper

in the Journal of the American Medical Association (JAMA) in 2004 explaining that "the methods described herein for increasing the percentage of cell-free fetal DNA provide a solid foundation for the development of a noninvasive prenatal diagnostic test." (Ex. 27 at 8 (Dhallan R., Au W., et al. *Methods to Increase the Percentage of Free Fetal DNA Recovered From the Maternal Circulation* JAMA 2004; 291(9):1114–1119, available at https://doi.org/10.1001/jama.291.9.1114).)

30. *JAMA* also ran an editorial alongside Dr. Dhallan's article in 2004, recognizing the significance of his invention to applications in prenatal genetic diagnosis and cancer detection and surveillance:

> In this issue of THE JOURNAL, the findings reported in the study by Dhallan and colleagues on enhancing recovery of cell-free DNA in maternal blood have major clinical implications. Developing a reliable, transportable technology for cell-free DNA analysis impacts 2 crucial areas—prenatal genetic diagnosis and cancer detection and surveillance. In prenatal genetic diagnosis, detecting a fetal abnormality without an invasive procedure (or with fewer invasive procedures) is a major advantage. Likewise in cancer surveillance (e.g., in patients with leukemia), monitoring treatment without having to perform a bone marrow aspiration for karyotype also would be of great benefit
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> * * *
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> With prospective studies focusing on clinical applications of these findings, profound clinical implications could emerge for prenatal diagnosis and cancer surveillance.

(Ex. 28 at 1, 3 (Simpson J.L., Bischoff F., *Cell-Free Fetal DNA in Maternal Blood: Evolving Clinical Applications* JAMA 2004; 291(9):1135–1137, available at https://doi.org/10.1001/jama.291.9.1135).)

31. In 2007, Dr. Dhallan published a second journal article in The Lancet that presented a study showcasing Ravgen's ability to use its novel technology to detect Down's syndrome using free fetal DNA in a maternal blood sample. (Ex. 29 (Dhallan R., Guo X., et al. *A non-invasive test*

for prenatal diagnosis based on fetal DNA present in maternal blood: a preliminary study. LANCET. 2007; 369(9560):474-481, available at https://doi.org/10.1016/S0140-6736(07)60115-9).) Dr. Dhallan's peers at the *Lancet* also recognized that his innovative test "opens a new era in prenatal screening." (*See* Ex. 30 (Benachi A., Costa J.M., *Non-invasive prenatal diagnosis of fetal aneuploidies* THE LANCET, 2007; 369(9560):440–442, available at https://doi.org/10.1016/S0140-6736(07)60116-0).)

32. Dr. Dhallan's publications received worldwide press coverage, from outlets such as CNN, BBC, and Washington Post. (*See* Ex. 31 (L. Palmer, "A better prenatal test?", CNN MONEY, Sept. 12, 2007, available at https://money.cnn.com/2007/09/07/smbusiness/amniocentesis.fsb/index.htm); Ex. 32 ("Hope for safe prenatal gene test" BCC NEWS, Feb 2, 2007, available at http://news.bbc.co.uk/2/hi/health/6320273.stm); Ex. 33 (A. Grander, "Experimental Prenatal Test Helps Spot Birth Defects", WASHINGTON POST, Feb. 2, 2007, available at https://www.washingtonpost.com/wp-dyn/content/article/2007/02/02/AR2007020200914.html).)

33. The Patents-in-Suit resulted from Dr. Dhallan's years-long research at Ravgen to develop these innovative new methods for detecting genetic disorders.

PATENTS-IN-SUIT

34. Ravgen incorporates by reference paragraphs 1–33.

35. The '277 Patent, entitled "Methods For Detection Of Genetic Disorders," was duly and legally issued by the United States Patent and Trademark Office on February 19, 2008. The inventor of the patent is Ravinder S. Dhallan, and the patent is assigned to Ravgen. A copy of the '277 Patent is attached hereto as Exhibit 1.

36. Ravgen is the exclusive owner of all rights, title, and interest in the '277 Patent, and has the right to bring this suit to recover damages for any current or past infringement of the '277 Patent. (*See* Ex. 3.)

37. The '720 Patent, entitled "Methods For Detection Of Genetic Disorders," was duly and legally issued by the United States Patent and Trademark Office on June 1, 2010. The inventor of the patent is Ravinder S. Dhallan, and the patent is assigned to Ravgen. A copy of the '720 Patent is attached hereto as Exhibit 2.

38. Ravgen is the exclusive owner of all rights, title, and interest in the '720 Patent, and has the right to bring this suit to recover damages for any current or past infringement of the '720 Patent. (*See* Ex. 4.)

39. The '277 Patent is directed to, among other things, novel methods used in the detection of genetic disorders. For example, claim 81 of the '277 Patent recites:

> A method for preparing a sample for analysis comprising isolating free fetal nucleic acid from a the sample, wherein said sample comprises an agent that inhibits lysis of cells, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor.

40. The '720 Patent is directed to novel methods for detecting a free nucleic acid in a sample. For example, claim 1 of the '720 Patent recites:

> A method for detecting a free nucleic acid, wherein said method comprises: (a) isolating free nucleic acid from a non-cellular fraction of a sample, wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor; and (b) detecting the presence or absence of the free nucleic acid.

41. The Patents-in-Suit are directed to unconventional, non-routine techniques for preparing and analyzing extracellular circulatory DNA, including for the detection of genetic

disorders. The Patents-in-Suit explain that, *inter alia*, the inventions claimed therein overcame problems in the field—for example, that the low percentage of fetal DNA in maternal plasma makes using the DNA for genotyping the fetus difficult—with a novel and innovative solution—the addition of cell lysis inhibitors, cell membrane stabilizers or cross-linkers to the maternal blood sample, which increase the percentage of cell-free DNA available for detection and analysis:

> The percentage of fetal DNA in maternal plasma is between 0.39-11.9% (Pertl, and Bianchi, *Obstetrics and Gynecology* 98: 483-490 (2001)). **The majority of the DNA in the plasma sample is maternal, which makes using the DNA for genotyping the fetus difficult**. However, methods that increase the percentage of fetal DNA in the maternal plasma allow the sequence of the fetal DNA to be determined, and allow for the detection of genetic disorders including mutations, insertions, deletions, and chromosomal abnormalities. **The addition of cell lysis inhibitors, cell membrane stabilizers or cross-linkers to the maternal blood sample can increase the relative percentage of fetal DNA.** While lysis of both maternal and fetal cells is inhibited, the vast majority of cells are maternal, and thus by reducing the lysis of maternal cells, there is a relative increase in the percentage of free fetal DNA.

(Ex. 1 ('277 Patent) at 32:24–39; Ex. 2 ('720 Patent) at 33:31–46 (emphasis added).)

42. The Patents-in-Suit teach that the benefit of Dr. Dhallan's discovery, an increase in the relative percentage of cell-free DNA, is realized by performance of the claimed method, including through the inclusion of an agent that inhibits the lysis of the cells in a sample:

> An overall increase in fetal DNA was achieved by reducing the maternal cell lysis, and thus, reducing the amount of maternal DNA present in the sample. In this example, formaldehyde was used to prevent lysis of the cells, however any agent that prevents the lysis of cells or increases the structural integrity of the cells can be used. The increase in fetal DNA in the maternal plasma allows the sequence of the fetal DNA to be determined, and provides for the rapid detection of abnormal DNA sequences or chromosomal abnormalities including but not limited to point mutation, reading frame shift, transition, transversion, addition, insertion, deletion, addition-deletion, frame-shift, missense, reverse mutation, and microsatellite alteration, trisomy, monosomy, other aneuploidies,

> amplification, rearrangement, translocation, transversion, deletion, addition, amplification, fragment, translocation, and rearrangement.

(Ex. 1 ('277 Patent) at 91:44–60; Ex. 2 ('720 Patent) at 92:10–26.)

43. For example, during the prosecution of the '720 Patent at the Patent and Trademark Office, Ravgen explained that the innovative concept of using agents that inhibit cell lysis during cell-free DNA detection and analysis is recited by the claimed methods of the '720 Patent, including in claim 1:

> Applicant has discovered that the addition of a cell lysis inhibitor to a sample prior to detecting the presence of free nucleic acid can ***significantly and unexpectedly*** increase the proportion of free nucleic acid obtained from the non-cellular fraction of a sample.
>
> * * *
>
> The methods disclosed in claims 1-8, 21-23, and 26 serve a long-felt need in the medical community, and provide unexpected results, and are therefore non-obvious.

(Ex. 5 ('720 File History, June 2, 2009 Response to Office Action) at 12, 14 (emphasis added).)

44. The inventive concept of the Patents-in-Suit of including an agent that inhibits cell lysis—for example, a membrane stabilizer, a cross-linker, and/or a cell lysis inhibitor—with a sample represented a significant improvement in the preparation of samples used for non-invasive testing, including non-invasive prenatal testing to unmask previously undetectable fetal genetic traits. At the time of the invention, it would not have been routine or conventional to add an agent that inhibits cell lysis to a sample to increase the proportion of free nucleic acid obtained from the non-cellular fraction of a sample. In fact, as described above, that inventive concept was recognized by Dr. Dhallan's peers as "an important step in improving detection of cell-free DNA." (Ex. 28 at 3.)

DEFENDANTS' INFRINGING ACTIVITIES

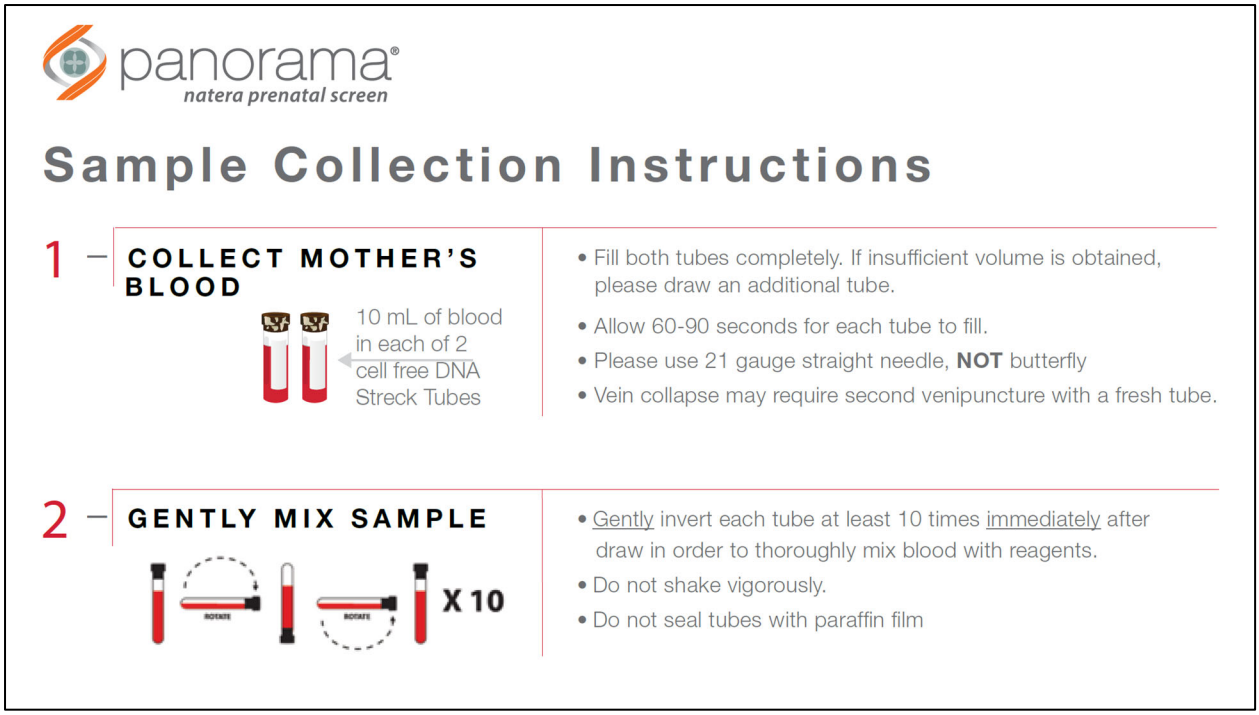
45. Ravgen incorporates by reference paragraphs 1–44.

A. The Accused Panorama Test

46. On March 1, 2013, Defendants launched the Panorama test, a commercial non-invasive prenatal test for detecting fetal genetic abnormalities. (*See* Ex. 34 at 1 ("Natera Launches Non-Invasive Prenatal Test Panorama™ with Best-in-Class Sensitivity, Specificity for Detection of Fetal Chromosomal Abnormalities," available at http://investor.natera.com/static-files/e8a10798-0960-45b6-909a-bc96cf9ea9f7) ("Natera, a leading innovator in reproductive and prenatal genetic testing, today [February 20, 2013] announced that the company's non-invasive prenatal screening test, Panorama™, will launch on March 1 for the detection of trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome) and select sex chromosome abnormalities, such as monosomy X (Turner's syndrome).").)

47. The Panorama test "uses fetal cell-free DNA found in maternal blood." (*Id.*; *see also* Ex. 35 at 25 (http://education.questdiagnostics.com/presentations/noninvasive-prenatal-testing-separate-but-not-equal?presentation_id=242).)

48. The Panorama test requires samples containing an agent that inhibits cell lysis. For example, Defendants instruct that "Panorama requires two cell-free DNA Streck tubes each filled with at least 10mL of the mother's blood." (Ex. 36 at 1 (https://www.natera.com/products/panorama-test?page=4).)

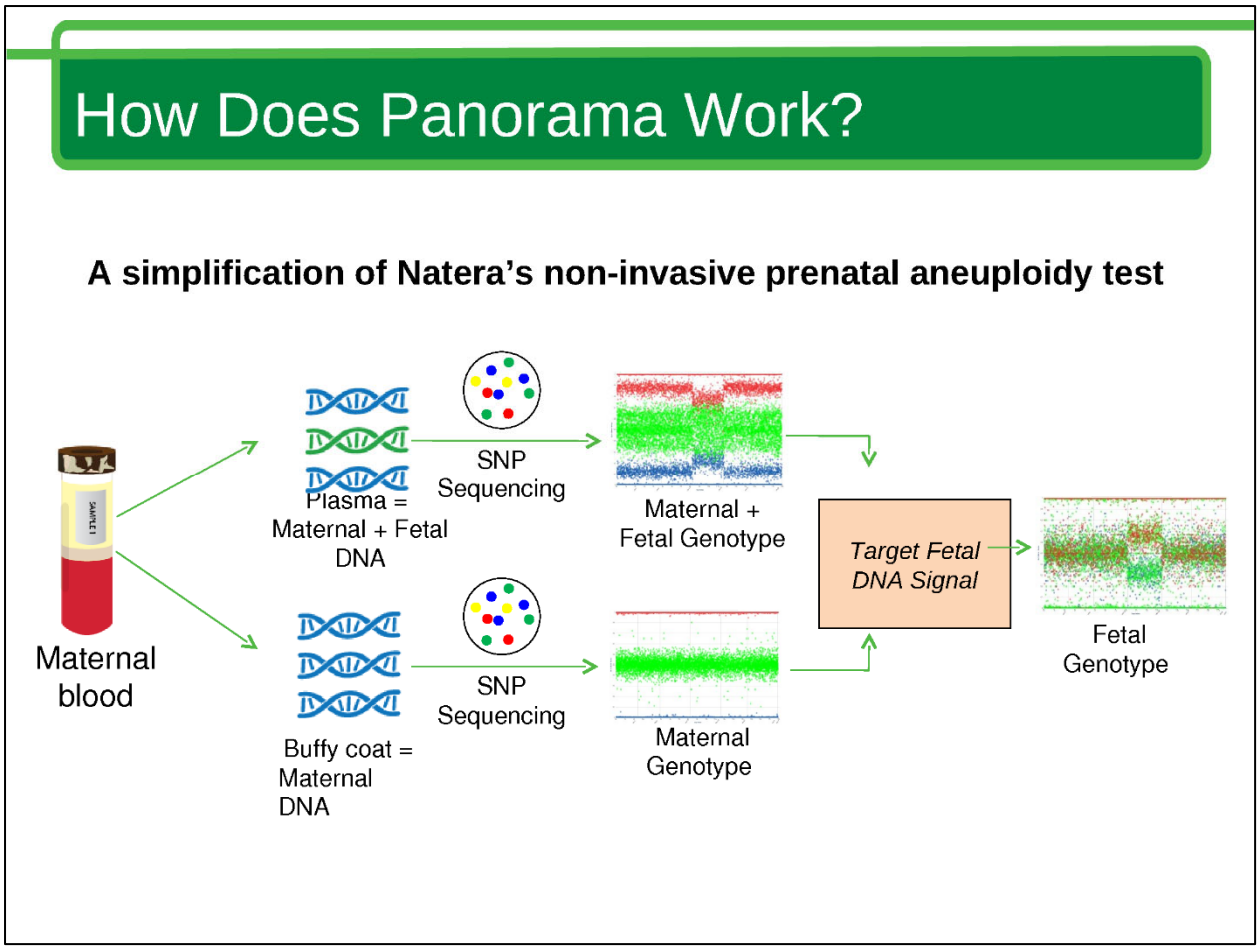


(Ex. 37 at 1 ("Panorama Sample Collection Instructions," downloaded from https://www.natera.com/file/7891/download?token=udKvGAKP).) In fact, the Panorama tests require the use of Streck cell-free DNA tubes for sample collection. *See* Ex. 38 at 43 (Natera, Inc. Form 10-K Filing (Filed March 2, 2020), https://natera.gcs-web.com/static-files/567cdba4-a6f4-4935-9329-3756d7e37226) ("Streck is the sole supplier of the blood collection tubes included in our Panorama test under a supply arrangement with Streck under which we are required to exclusively use Streck tubes.").)

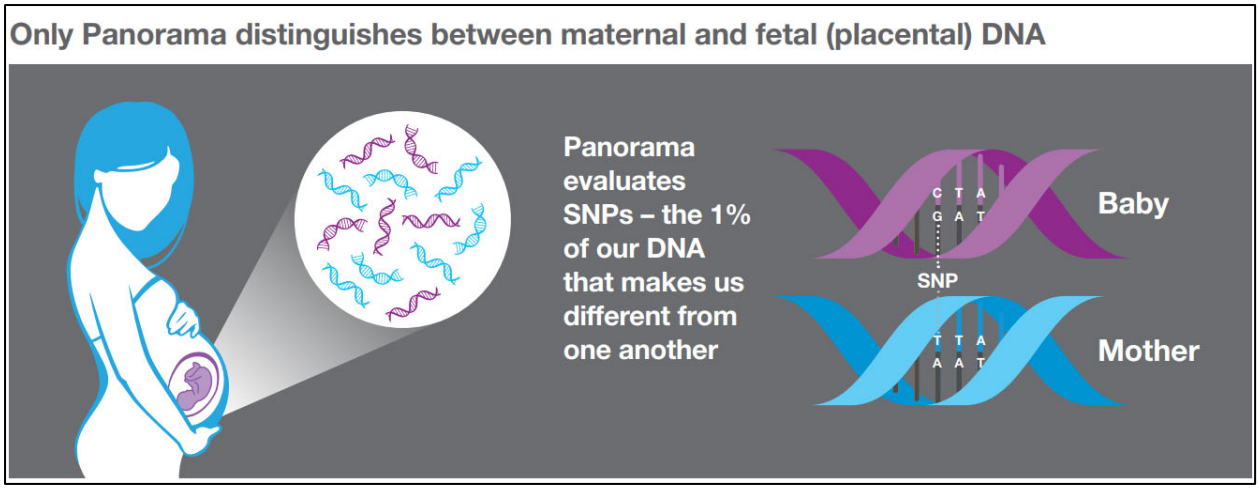
49. The Streck Cell-Free DNA Blood Collection Tube ("BCT") includes an agent that inhibits cell lysis. A Streck Cell-Free DNA BCT "stabilizes nucleated blood cells. The unique preservative ***limits the release of genomic DNA, allowing isolation of high-quality cell-free DNA***. Cell-Free DNA BCT has also been demonstrated to minimize the degradation of circulating tumor cells (CTCs). By ***limiting cell lysis***, the specialized chemistry provides sample integrity during storage, shipping and handling of blood samples. Cell-free DNA and gDNA are stable for

up to 14 days at 6 °C to 37 °C. CTCs are stable for up to 7 days at 15 °C to 30 °C." (Ex. 39 at 2 (https://www.streck.com/products/stabilization/cell-free-dna-bct/#resources).)

50. In processing Panorama tests, Defendants isolate cell-free DNA from a sample of maternal blood collected in a Streck Cell-Free DNA BCT and then analyze the isolated fetal cell-free DNA to detect chromosomal abnormalities as shown below:



(Ex. 35 at 25.)



(Ex. 40 at 2 (https://www.natera.com/sites/default/files/PAN-MD-BR_2018_02_14_NAT-801513_DWNLD.pdf); *see also, e.g.*, Ex. 41 at 1 (https://www.natera.com/press-releases/panorama-nipt-achieves-2-million-test-milestone) ("Panorama reveals a baby's risk for severe genetic disorders as early as nine weeks into pregnancy. The test uses a unique single-nucleotide polymorphism (SNP)-based technology to analyze fetal/placental DNA obtained through a blood draw from the mother. It is the only test that differentiates between maternal and fetal DNA in the relevant chromosomes of interest."); Ex. 42 at 2 (https://www.natera.com/womens-health/panorama-clinician-info) (displaying video entitled, "Panorama: The Power of SNPs," stating at 00:04–00:30: "Panorama is a non-invasive prenatal screening test, or NIPT, from Natera. It screens fetal DNA from the placenta for common chromosome conditions, such as aneuploidies and microdeletions. Panorama and other NIPTs isolate cell-free DNA from maternal blood. While other NIPTs utilize quantitative methods, Panorama analyzes single nucleotide polymorphisms, or SNPs, to determine the risk of certain chromosome abnormalities in the fetus."); *id.* at 01:00–01:25 ("The plasma from the maternal DNA sample contains a mixture of maternal DNA fragments as well as fetal DNA fragments derived from the placenta. Another component of the blood sample is the buffy coat, which

contains only maternal white blood cells. By analyzing the SNPs in the plasma, which contain a combination of maternal and fetal DNA fragments, as well as the buffy coat which contains only maternal DNA, Panorama is able to isolate the fetal DNA signal, and analyze it for chromosome abnormalities."); Ex. 43 at 1 (Hall, M. P., et al *Non-invasive prenatal detection of trisomy 13 using a single nucleotide polymorphism- and informatics-based approach* PLOS ONE, 2014; 9(5), e96677, https://doi.org/10.1371/journal.pone.0096677) (Natera, Inc. study describing the technology underlying the Panorama explains the protocol to include that "[c]ell-free DNA was isolated from maternal plasma, amplified in a single multiplex polymerase chain reaction assay that interrogated 19,488 SNPs covering chromosomes 13, 18, 21, X, and Y, and sequenced."); Ex. 38 at 8 ("We extract DNA from each sample, amplify the specific SNPs that we are interested in measuring, and then sequence the DNA using NGS. Using our proprietary bioinformatics technology, we analyze the DNA sequences to assess the state of the fetal genome, focusing on the SNP data, while incorporating public information from the Human Genome Project. Our bioinformatics algorithm builds billions of detailed models of the potential genetic state of the sample to determine the most likely diagnosis. After Panorama generates its result, we provide the doctor or the laboratory with a simple report showing the risk that abnormalities are present in the fetus."); *see generally* Ex. 44 (https://www.natera.com/snp-method-nipt).)

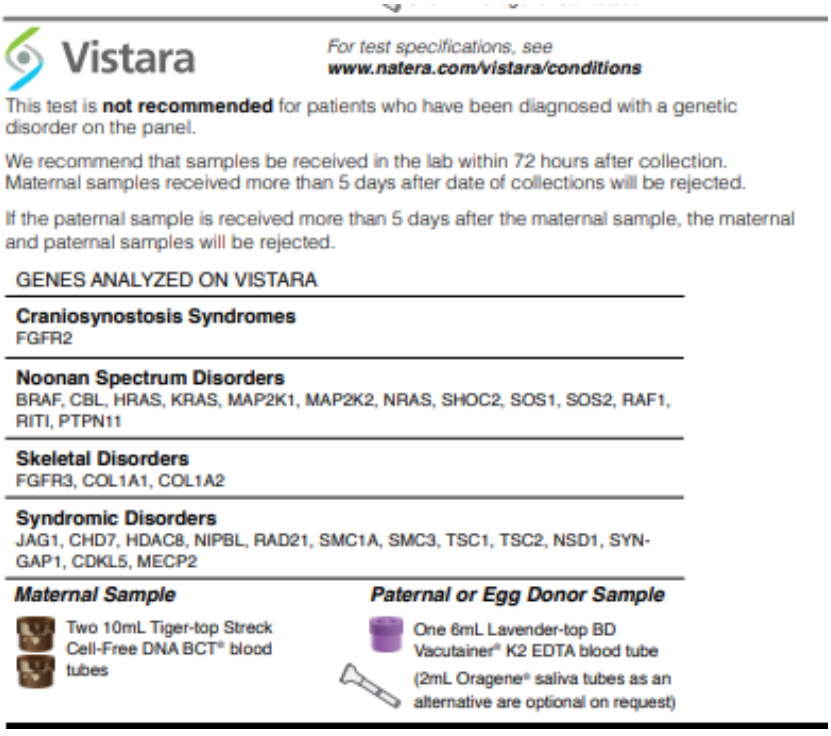
B. The Accused Vistara Test

51. May 2017, Defendants launched the Vistara test, a commercial non-invasive prenatal test for detecting fetal genetic abnormalities. (*See* Ex. 45 at 1 ("Natera, Inc. Announces Launch of Vistara Single-Gene Mutation NIPT," available at https://natera.gcs-web.com/news-releases/news-release-details/natera-inc-announces-launch-vistara-single-gene-mutation-nipt) ("Natera (NASDAQ: NTRA), a leader in genetic testing, announced the launch of Vistara, a non-

invasive prenatal test (NIPT) to screen single-gene disorders. Vistara is a complement to Natera's market-leading Panorama® non-invasive prenatal test (NIPT) and screens for new mutations in 30 genes that have a combined incidence rate of nearly 1 in 600, which is higher than that of Down syndrome."); Ex. 25 at 68 ("We began offering our Vistara single-gene mutations screening test in May 2017.").)

52. The Vistara test uses "circulating cell-free fetal DNA in maternal blood." (Ex. 46 at 1 (https://zotzklimas.de/images/vistara/VISTARA_White_Paper_englisch.pdf); *see* Ex. 47 at 2 (http://www.elitekliinik.ee/eng/wp-content/uploads/sites/3/2018/10/POSITIVE-Vistara-Sample-Report.pdf) (sample Natera Vistara report stating that Vistara "evaluates genetic information in the maternal blood, which is a mixture of maternal and placental DNA").)

53. The Vistara test requires samples containing an agent that inhibits cell lysis. For example, Defendants instruct that Vistara requires a maternal sample collected in "[t]wo 10mL Tiger-top Streck Cell-Free DNA BCT® blood tubes":



Vistara

For test specifications, see ***www.natera.com/vistara/conditions***

This test is **not recommended** for patients who have been diagnosed with a genetic disorder on the panel.

We recommend that samples be received in the lab within 72 hours after collection. Maternal samples received more than 5 days after date of collections will be rejected.

If the paternal sample is received more than 5 days after the maternal sample, the maternal and paternal samples will be rejected.

GENES ANALYZED ON VISTARA

Craniosynostosis Syndromes
FGFR2

Noonan Spectrum Disorders
BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, SHOC2, SOS1, SOS2, RAF1, RITI, PTPN11

Skeletal Disorders
FGFR3, COL1A1, COL1A2

Syndromic Disorders
JAG1, CHD7, HDAC8, NIPBL, RAD21, SMC1A, SMC3, TSC1, TSC2, NSD1, SYNGAP1, CDKL5, MECP2

Maternal Sample	***Paternal or Egg Donor Sample***
Two 10mL Tiger-top Streck Cell-Free DNA BCT® blood tubes	One 6mL Lavender-top BD Vacutainer® K2 EDTA blood tube (2mL Oragene® saliva tubes as an alternative are optional on request)

(Ex. 48 at 2 ("Vistara Sample Collection Instructions," available at https://www.natera.com/sites/default/files/UNIV-13%20NAT-802095_FILLABLE.pdf.)

54. As described above, samples collected in Streck Cell-Free DNA BCT tubes, including Signatera blood samples, contain an agent that inhibits cell lysis. (*See* Ex. 39 at 2.)

55. In processing Vistara tests, cell-free DNA is isolated from a sample of maternal blood collected in a Streck Cell-Free DNA BCT, and then the isolated fetal cell-free DNA is analyzed to detect single gene disorders. (Ex. 46 at 1 ("[The Vistara test] screens for specific clinically significant and life-altering single gene disorders that are outside the scope of current non-invasive prenatal tests. A SNP-based fetal fraction calculation method was developed that yielded concordance with the established Y-chromosome method. We also demonstrate that this test can detect DNA changes in cell-free plasma DNA using a combination of spike-in samples and samples from pregnant women."); *id.* at 2 ("plasma cell-free DNA is extracted from maternal blood"); *id.* ("For this assay, fetal fraction is calculated based on the detection of the unique SNPs analyzed across the genome."); *id.* at 5 ("This assay can accurately sequence cell-free DNA for the mother's plasma and can detect DNA changes (both benign and disease-causing) with a sensitivity and specificity >99%.").)

56. Defendants instruct third-party laboratories to perform the Vistara tests as described above. (Ex. 38 at 40 ("[O]ur Vistara single-gene mutations testing is performed by third-party laboratories. These third-party laboratories are subject to contractual obligations to perform these services for us."); Ex. 46 at 5 ("Natera collaborated with Baylor Genetics to assist in clinical introduction of the test, particularly in providing samples to help establish the lower limit of fetal fraction. This test is performed and reported by Baylor Genetics.").)

C. The Accused Signatera Test

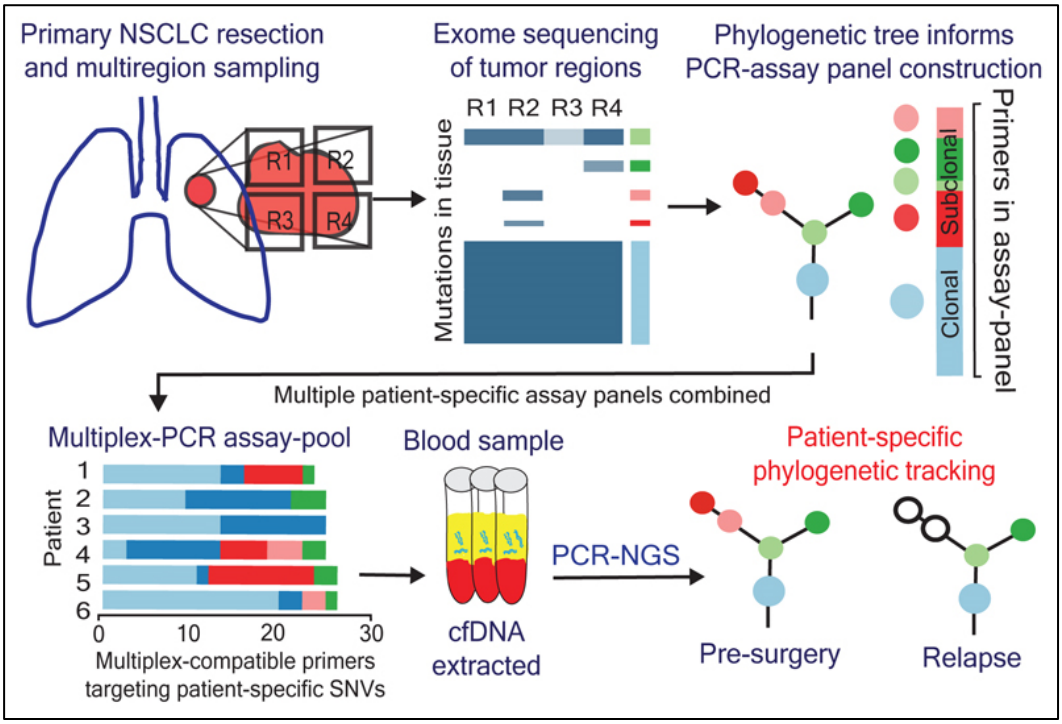
57. In 2017, Defendants launched the Signatera test, a circulating tumor (ctDNA) blood test for Minimal Residual Disease (MRD) assessment and surveillance of disease recurrence in patients previously diagnosed with cancer. (*See* Ex. 49 at 1 ("Natera Launches Signatera™ Personalized Circulating Tumor DNA Technology for Cancer Research," available at https://www.natera.com/press-releases/natera-launches-signatera%E2%84%A2-personalized-circulating-tumor-dna-technology-cancer) ("Natera, Inc. (NASDAQ: NTRA), a leader in non-invasive genetic testing, today [August 21, 2017] announced the launch of Signatera™, a circulating tumor DNA (ctDNA) technology that analyzes and tracks mutations specific to an individual's tumor, for research use only (RUO) by oncology researchers and biopharmaceutical companies. Already in clinical validation with multiple world-leading cancer institutes, Signatera™ offers a novel personalized approach to cancer detection in plasma.").)

58. The Signatera test involves extracting circulating tumor DNA (ctDNA) from a blood sample for detection. (*Id.*)

59. The Signatera test requires samples containing an agent that inhibits cell lysis. For example, Defendants instruct that the blood sample for the Signatera test be collected in "Two tubes of whole blood collected in Streck tubes or 10 mL of double-spun plasma." (Ex. 50 at 5 (https://www.natera.com/oncology/signatera-research-pipeline); *see* Ex. 36 at 43 ("We also only use Streck tubes for the primary analysis of Signatera results"); Ex. 51 at 1 (https://www.natera.com/sites/default/files/SGN_PositiveReport_Mockup.pdf) (Signatera report describing that "Circulating tumor DNA is extracted from plasma collected in Streck tubes using Natera's proprietary methods").)

60. As described above, samples collected in Streck Cell-Free DNA BCT tubes, including Signatera blood samples, contain an agent that inhibits cell lysis. (*See* Ex. 39 at 2.)

61. In processing Signatera tests, Defendants isolate and sequence cell-free tumor DNA from the blood sample:



(Ex. 52 at 2 (Abbosh C. et al. *Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution* NATURE 2017; 545(7655): 446-451, https://doi.org/10.1038/nature22364, Figure 1) ("Overview of the study methodology. . . . Cell-free DNA was extracted from pre- and post-operative plasma samples and multiplex-PCR performed, followed by sequencing of amplicons."); *see also, e.g.*, Ex. 50 at 4 ("Signatera residual disease test. The DNA sequence from your tumor tissue is compared to normal cells from your blood to determine the unique set of mutations specific to your tumor tissue."); Ex. 51 at 1 ("Whole-exome sequencing using KAPA Hyper Prep library kit (Roche) with a custom xGen exome capture (IDT) is performed to identify tumor DNA sequence using a proprietary algorithm. Sixteen putative clonal variants present in the tumor but absent in the baseline DNA form the basis for individual-specific PCR-based assays. Individual-specific PCR assays are run to detect presence or absence of circulating tumor DNA (ctDNA). A

patient's plasma sample is considered ctDNA positive when at least two individual-specific tumor variants are detected.").)

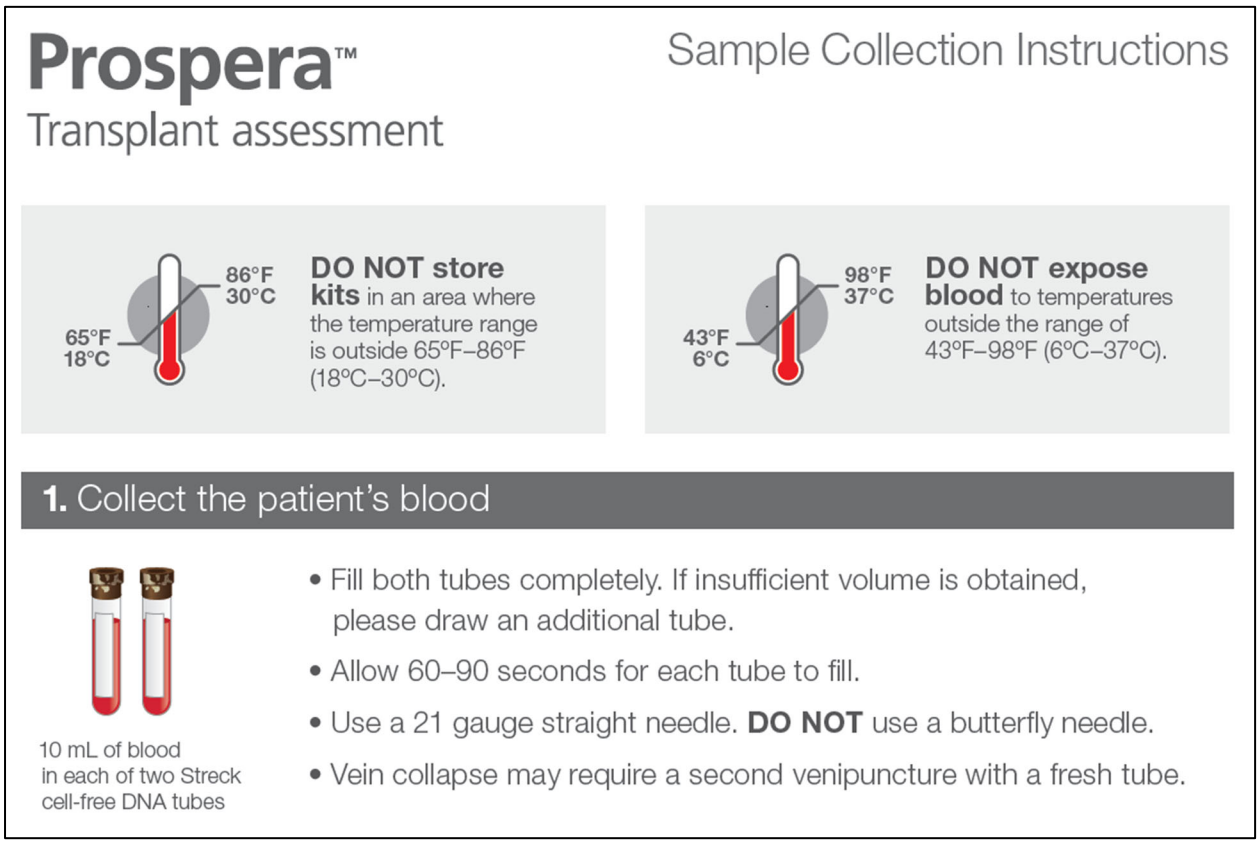
D. The Accused Prospera Test

62. In 2020, Defendants launched the Prospera test, a donor-derived cell-free DNA (dd-cfDNA) test for assessing the risk of allograft rejection. (*See* Ex. 38 at 16 ("We received a final Medicare local coverage determination, or LCD, for Prospera in December 2019, covering all kidney transplant recipients, including those with multiple kidney transplants, and are working towards a full-scale commercial launch in 2020."); Ex. 58 at 1 ("Natera Receives Final Medicare Coverage for Prospera™ Organ Transplant Rejection Assessment Test," available at https://www.natera.com/press-releases/natera-receives-final-medicare-coverage-prospera%E2%84%A2-organ-transplant-rejection) ("The Prospera test assesses the risk of active renal allograft rejection with greater precision than other biomarkers or other dd-cfDNA tests on the market.").)

63. The Prospera test is used to detect the presence of donor-derived cell-free DNA in blood samples of organ recipients, which can indicate whether the recipient is experiencing active rejection. (*See* Ex. 17 at 1 (https://www.natera.com/organ-transplantation/prospera-organ-transplantation-assessment) ("Prospera is powered by highly optimized, proprietary cell-free DNA (cfDNA) technology. As part of your toolkit to watch for signs of active rejection, Prospera assesses all types of kidney transplant rejection with great precision. . . . Simpler and less invasive than biopsy: Prospera measures the amount of donor DNA from a transplant recipient through a blood test.").)

64. The Prospera test requires samples containing an agent that inhibits cell lysis. For example, Defendants require that the blood sample for Prospera be collected in Streck Cell-Free

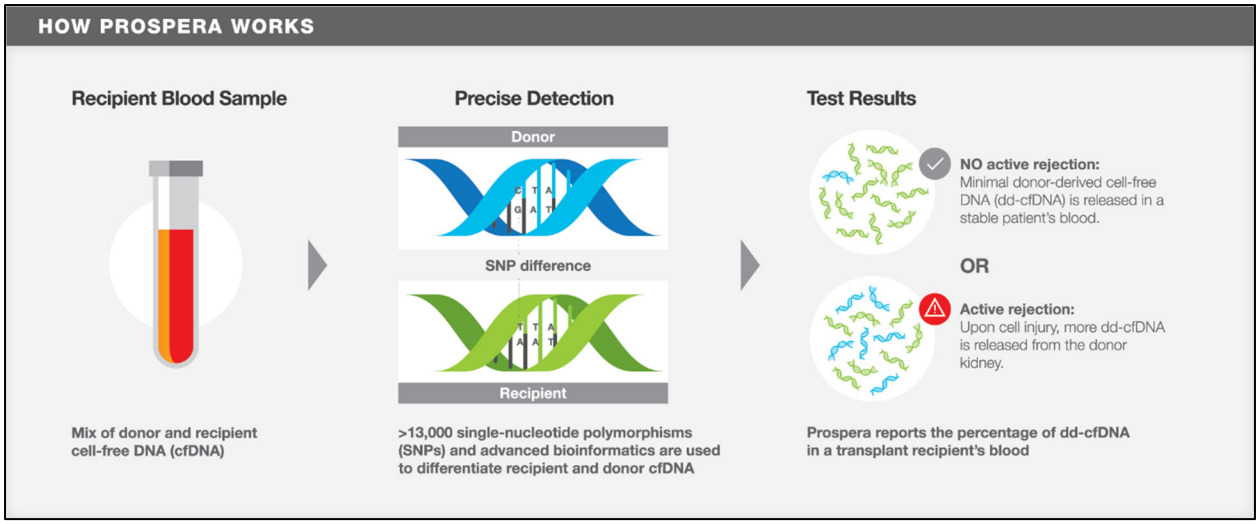
DNA tubes. (*See* Ex. 54 at 2 (https://www.natera.com/organ-transplantation/prospera-faq) ("Prospera requires two cell-free DNA Streck tubes each filled with at least 10mL of the patient's blood to achieve optimal performance.").)



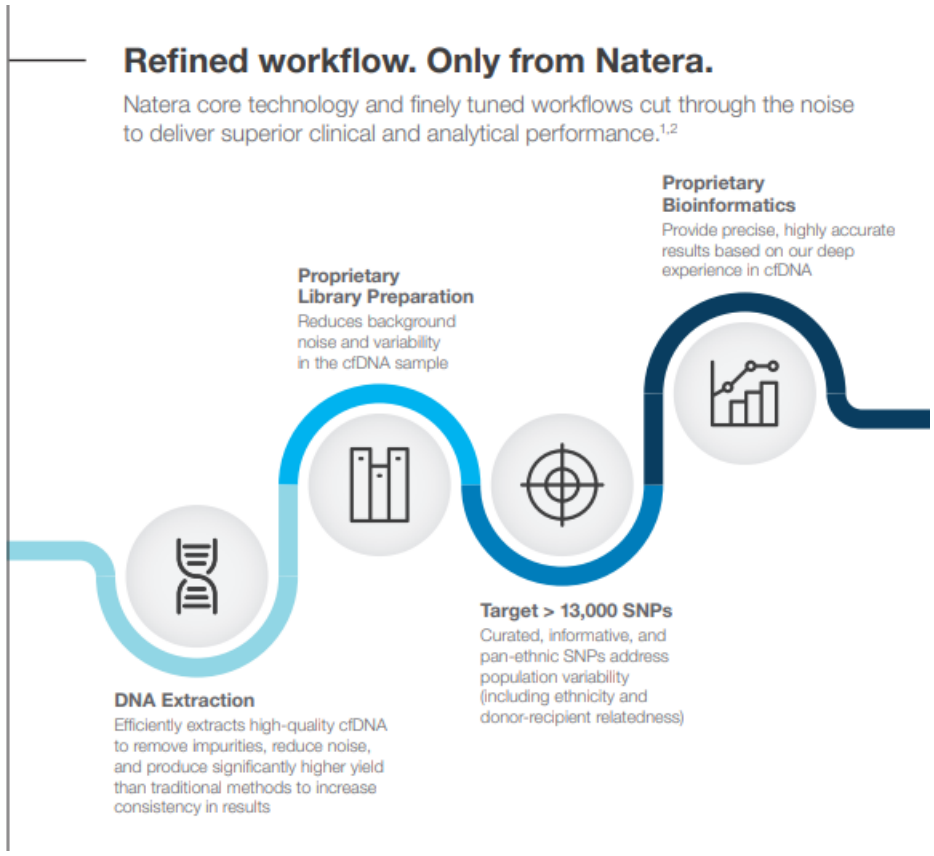
(Ex. 55 at 1 ("Prospera Sample Collection Instructions," available at https://www.natera.com/sites/default/files/MLB-10096-Rev01%20Prospera%20Domestic%20Sample%20Collection%20Instructions-NAT-801960_DWNLD_REVISION%20FOR%20OCT%202019.pdf); *see also* Ex. 38 at 43 ("We also only use Streck tubes . . . for our Prospera test.").)

65. As described above, samples collected in Streck Cell-Free DNA BCT tubes, including Signatera blood samples, contain an agent that inhibits cell lysis. (*See* Ex. 39 at 2.)

66. In processing Prospera tests, Defendants isolate and sequence cell-free DNA from the blood sample.



(Ex. 17 at 2.)



(Ex. 53 at 2 (https://www.natera.com/sites/default/files/PRO_PhysicianBrochure_20190903_NAT-801997_Alternate_DWNLD.pdf); Ex 53 at 1 ("Prospera is powered by highly optimized, proprietary cell-free DNA (cfDNA) technology. As part of your toolkit to watch for

signs of active rejection, Prospera assesses all types of kidney transplant rejection with great precision. . . . Simpler and less invasive than biopsy: Prospera measures the amount of donor DNA from a transplant recipient through a blood test."); *see also* Ex. 38 at 16 ("Our assay, Prospera, is designed to assess active rejection in patients who have undergone kidney transplantation by measuring the fraction of dd-cfDNA in the recipient's blood, which can spike relative to background cfDNA when the transplanted organ is injured due to immune rejection."); Ex. 56 at 3 (Sigdel T.K. et al. *Optimizing Detection of Kidney Transplant Injury by Assessment of Donor-Derived Cell-Free DNA via Massively Multiplex PCR* J CLIN MED. 2018; 8(1):19, available at https://doi.org/10.3390/jcm8010019)[1] ("**dd-cfDNA Measurement in Blood Samples**. Cell-free DNA was extracted from plasma samples using the QIAamp Circulating Nucleic Acid Kit (Qiagen) and quantified on the LabChip NGS 5k kit (Perkin Elmer, Waltham, MA, USA) following manufacturer's instructions. Cell-free DNA was input into library preparation using the Natera Library Prep kit as previously described, with a modification of 18 cycles of library amplification to plateau the libraries. Purified libraries were quantified using LabChip NGS 5k as previously described. Target enrichment was accomplished using massively multiplexed-PCR (mmPCR) using a modified version of a previously described method, with 13,392 single nucleotide polymorphisms (SNPs) targeted. Amplicons were then sequenced on an Illumina HiSeq 2500 Rapid Run, 50 cycles single end, with 10–11 million reads per sample."); *id*. at 16 ("In conclusion, this study validates the use of dd-cfDNA in the blood as an accurate marker of kidney injury/rejection across a range of pathologies with acute and chronic findings.").)

[1] Defendants reference this paper as a "Clinical Validation Study" for Prospera. (*See* Ex. 57 at 3 (https://www.natera.com/organ-transplantation/prospera-clinicians).)

E. Defendants' Knowledge Of The Ravgen Patents

67. On information and belief, Defendants have been aware of the Patents-in-Suit and the fact that performance of the Defendants' cell-free DNA tests, including Panorama, Vistara, Signatera, and Prospera, practice the claimed inventions of those patents since at least 2015.

68. In 2014 and 2015, Matthew Rabinowitz, Natera, Inc.'s co-founder, former Chief Executive Officer and current Executive Chairman and NSTX, Inc.'s Chief Executive Officer, and Daniel Rabinowitz, Natera, Inc.'s Secretary and General Counsel, communicated with Dr. Dhallan, the founder of Ravgen, about Ravgen's technology and its patent portfolio.

69. For example, in January 2014, Defendants, through Matthew Rabinowitz and Daniel Rabinowitz, reached out to Dr. Dhallan via email and expressed interest in meeting regarding Ravgen's technology. In 2015, the same individuals, on behalf of Natera Inc., communicated with Dr. Dhallan about the Ravgen patent portfolio through email correspondence, phone calls, and an in-person meeting. As referenced in a letter dated June 25, 2015 from Dr. Dhallan to Matthew Rabinowitz and Daniel Rabinowitz, those individuals expressed interest in licensing or acquiring Ravgen's patent portfolio. (*See, e.g.*, Ex. 6 at 1.) The Ravgen patent portfolio—both at that time and today—is composed of seven U.S. Patents, including the two Patents-in-Suit. On information and belief, at least by June 2015, Defendants were therefore aware of the Patents-in-Suit and were aware of, or willfully blind to, their infringement of those patents.

70. On May 15, 2020, Ravgen, through outside counsel, sent another letter to Matthew Rabinowitz and Daniel Rabinowitz, identifying the '720 and '277 Patents and informing Defendants that "Natera has used and continues to use its patent technology by making, using, selling, offering to sell, and/or importing products that include the patented methods, such as, for example, Natera's Panorama test." (*See* Exs. 7–8.) Although that letter requested a meeting to discuss a potential license, Defendants failed to respond. (*Id.*)

71. Despite their knowledge of the Patents-in-Suit and of their infringement of those patents by at least June 2015, Defendants have continued to willfully infringe the Patents-in-Suit so as to obtain the significant benefits of Ravgen's innovations without paying compensation to Ravgen. For example, Defendants have continued to use the claimed methods in their Panorama test without a license, generating hundreds of millions of dollars in revenue. Additionally, after becoming aware of the Patents-in-Suit, Defendants began commercializing three other cell-free DNA tests built on and including the claimed inventions, the Vistara, Signatera, and Prospera tests, which launched in 2017, 2017, and 2020 respectively.

COUNT I

(Infringement Of The '277 Patent)

72. Ravgen incorporates by reference paragraphs 1–71.

73. The '277 Patent is valid and enforceable.

74. Defendants have infringed, and continue to infringe, one or more claims of the '277 Patent under 35 U.S.C. § 271, either literally and/or under the doctrine of equivalents, by making, using, selling, and/or offering for sale in the United States, and/or importing into the United States, products and/or methods encompassed by those claims, including Defendants' Panorama and Vistara tests.

75. For example, Defendants infringe at least exemplary claim 81 of the '277 Patent by using the Panorama test. For example, use of the Panorama test requires a method for preparing a sample for analysis, wherein said method comprises:

a. isolating free fetal nucleic acid (such as cell-free fetal DNA) from a sample (such as a maternal blood sample) (*see, e.g.*, Ex. 42 at 2 (video describing isolation of cell-free fetal DNA from maternal blood sample)),

b. wherein said sample comprises an agent that inhibits lysis of cells, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor (such as cell-free DNA Streck tubes filled with at least 10mL of blood) (*see, e.g.*, Ex. 36 at 1 (describing that the Panorama test requires "two cell-free DNA Streck tubes each filled with at least 10mL of the mother's blood"); Ex. 39 at 2 (describing Streck cell-free DNA tubes as containing a "unique preservative [which] limits the release of genomic DNA, allowing isolation of high-quality cell-free DNA" and "specialized chemistry" that "***limit[s] cell lysis***")).

76. For example, Defendants infringe at least exemplary claim 81 of the '277 Patent by using the Vistara test and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Vistara test. For example, use of the Vistara test requires a method for preparing a sample for analysis, wherein said method comprises:

a. isolating free fetal nucleic acid (such as cell-free fetal DNA) from a sample (such as a maternal blood sample) (*see, e.g.*, Ex. 46 at 2 ("plasma cell-free DNA is extracted from maternal blood")),

b. wherein said sample comprises an agent that inhibits lysis of cells, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor (such as cell-free DNA Streck tubes filled with at least 10mL of blood) (*see, e.g.*, Ex. 48 at 2 (describing that Vistara requires a maternal sample collected in "[t]wo 10mL Tiger-top Streck Cell-Free DNA BCT® blood tubes"); Ex. 39 at 2 (describing Streck cell-free DNA tubes as containing a "unique preservative [which] limits the release of genomic DNA,

allowing isolation of high-quality cell-free DNA" and "specialized chemistry" that "***limit[s] cell lysis***")).

77. Defendants have infringed, and continue to infringe, one or more claims of the '277 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Panorama test and by using the Vistara test and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Vistara test.

78. Defendants have also induced infringement, and continue to induce infringement, of one or more claims of the '277 Patent under 35 U.S.C. § 271(b). Defendants actively, knowingly, and intentionally induced, and continue to actively, knowingly, and intentionally induce, infringement of the '277 Patent by selling or otherwise supplying the Vistara tests with the knowledge and intent that third-party laboratories will use the Vistara tests supplied by Defendants to infringe the '277 Patent; and with the knowledge and intent to encourage and facilitate third-party infringement through the dissemination of the Vistara tests and/or the creation and dissemination of promotional and marketing materials, supporting materials, instructions, product manuals, and/or technical information related to the Vistara tests.

79. Defendants specifically intended and were aware that the ordinary and customary use of the Vistara tests would infringe the '277 Patent. For example, Defendants sell and provide the Vistara tests, which when used in their ordinary and customary manner intended and instructed by Defendants, infringe one or more claims of the '277 Patent, including at least exemplary claim 81. Defendants further provide product manuals and other instructional materials that cause third-party laboratories to operate the Vistara tests for their ordinary and customary use. Defendants' third-party laboratories have directly infringed the '277 Patent, including at least exemplary claim 81, through the normal and customary use of the Vistara tests. Defendants accordingly have

induced and continue to induce Defendants' third-party laboratories to use the Vistara tests in their ordinary and customary way to infringe the '277 Patent, knowing, or at least being willfully blind to the fact, that such use constitutes infringement of the '277 Patent.

80. Defendants have contributed to the infringement by third parties, including Defendants' third-party laboratories, and continue to contribute to infringement by third parties, of one or more claims of the '277 Patent under 35 U.S.C. § 271(c), by making, selling and/or offering for sale in the United States, and/or importing into the United States, the Vistara tests, knowing that those products constitute a material part of the inventions of the '277 Patent, knowing that those products are especially made or adapted to infringe the '277 Patent, and knowing that those products are not staple articles of commerce suitable for substantial non-infringing use.

81. Defendants have had knowledge of and notice of the '277 Patent and their infringement since at least June 2015, as evidenced by communications between Ravgen and Defendants.

82. Defendants' infringement of the '277 Patent was, and continues to be, willful and deliberate since, at least June 2015, when Defendants' representatives communicated Defendants' interest in acquiring or licensing the Ravgen patent portfolio, including the '277 Patent.

83. Ravgen has been and continues to be damaged by Defendants' infringement of the '277 Patent, and will suffer irreparable injury unless the infringement is enjoined by this Court.

84. Defendants' conduct in infringing the '277 Patent renders this case exceptional within the meaning of 35 U.S.C. § 285.

COUNT II

Infringement Of The '720 Patent

85. Ravgen incorporates by reference paragraphs 1–84.

86. The ’720 Patent is valid and enforceable.

87. Defendants have infringed, and continue to infringe, one or more claims of the ’720 Patent under 35 U.S.C. § 271, either literally and/or under the doctrine of equivalents, by making, using, selling, and/or offering for sale in the United States, and/or importing into the United States, products and/or methods encompassed by those claims, including Defendants’ Panorama, Vistara, Signatera, and Prospera tests.

88. For example, Defendants infringe at least exemplary claim 1 of the ’720 patent by using the Panorama test. For example, use of the Panorama test requires a method for detecting a free nucleic acid, wherein said method comprises:

a. isolating free nucleic acid (such as cell-free fetal DNA) from a non-cellular fraction of a sample (such as a maternal blood sample) (*see, e.g.*, Ex. 42 at 2 (video describing isolation of cell-free fetal DNA from maternal blood sample)),

b. wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor (such as cell-free DNA Streck tubes filled with at least 10mL of maternal blood) (*see, e.g.*, Ex. 36 at 1 (describing that the Panorama test requires “two cell-free DNA Streck tubes each filled with at least 10mL of the mother’s blood”); Ex. 39 at 2 (describing Streck cell-free DNA tubes as containing a “unique preservative [which] limits the release of genomic DNA, allowing isolation of high-quality cell-free DNA” and “specialized chemistry” that “***limit[s] cell lysis***”)).

c. detecting the presence or absence of the free nucleic acid (*see, e.g.*, Ex. 46 at 5 (“This assay can accurately sequence cell-free DNA for the mother’s plasma and

can detect DNA changes (both benign and disease-causing) with a sensitivity and specificity >99%.")).

89. For example, Defendants infringe at least exemplary claim 1 of the '720 patent by using the Vistara test and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Vistara test. For example, use of the Vistara test requires a method for detecting a free nucleic acid, wherein said method comprises:

a. isolating free nucleic acid (such as cell-free fetal DNA) from a non-cellular fraction of a sample (such as a maternal blood sample) (*see, e.g.*, Ex. 46 at 2 ("plasma cell-free DNA is extracted from maternal blood")),

b. wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor (such as cell-free DNA Streck tubes filled with at least 10mL of maternal blood) (*see, e.g.*, Ex. 48 at 2 (describing that Vistara requires a maternal sample collected in "[t]wo 10mL Tiger-top Streck Cell-Free DNA BCT® blood tubes"); Ex. 39 at 2 (describing Streck cell-free DNA tubes as containing a "unique preservative [which] limits the release of genomic DNA, allowing isolation of high-quality cell-free DNA" and "specialized chemistry" that "***limit[s] cell lysis***")).

c. detecting the presence or absence of the free nucleic acid (*see, e.g.*, Ex. 46 at 1–5 (describing the detection of fetal DNA obtained from the maternal blood).

90. For example, Defendants infringe at least exemplary claim 1 of the '720 patent by using the Signatera test. For example, use of the Signatera test requires a method for detecting a free nucleic acid, wherein said method comprises:

a. isolating free nucleic acid (such as cell-free circulating tumor DNA) from a non-cellular fraction of a sample (such as a blood sample) (*see, e.g.*, Ex. 52 at 2 ("Cell-free DNA was extracted from pre- and post-operative plasma samples")),

b. wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor (such as cell-free DNA Streck tubes filled with blood) (*see, e.g.*, Ex. 50 at 5 ("Two tubes of whole blood collected in Streck tubes or 10 mL of double-spun plasma."); Ex. 39 at 2 (describing Streck cell-free DNA tubes as containing a "unique preservative [which] limits the release of genomic DNA, allowing isolation of high-quality cell-free DNA" and "specialized chemistry" that "***limit[s] cell lysis***"));

c. detecting the presence or absence of the free nucleic acid (*see, e.g.*, Ex. 50 at 4 ("The DNA sequence from your tumor tissue is compared to normal cells from your blood to determine the unique set of mutations specific to your tumor tissue.")).

91. For example, Defendants infringe at least claim 1 of the '720 patent by using the Prospera test. For example, use of the Prospera test requires a method for detecting a free nucleic acid, wherein said method comprises:

a. isolating free nucleic acid (such as donor-donated and recipient cell-free DNA) from a non-cellular fraction of a sample (such as a blood sample) (*see, e.g.*, Ex. 53 at 2 (the Prospera test "[e]fficiently extracts high-quality cfDNA to remove impurities, reduce noise, and produce significantly higher yield"; showing "mix of donor and recipient cell-free DNA" from blood sample)).

b. wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor (such as cell-free DNA Streck tubes filled with at least 10mL of blood) (*see, e.g.*, Ex. 54 at 2 ("Prospera requires two cell-free DNA Streck tubes each filled with at least 10mL of the patient's blood"); Ex. 39 at 2 (describing Streck cell-free DNA tubes as containing a "unique preservative [which] limits the release of genomic DNA, allowing isolation of high-quality cell-free DNA" and "specialized chemistry" that "***limit[s] cell lysis***"));

c. detecting the presence or absence of the free nucleic acid (*see, e.g.*, Ex. 17 at 1–2 (describing the detection of dd-cfDNA)).

92. Defendants have infringed, and continue to infringe, one or more claims of the '277 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Panorama, Signatera, and Prospera tests and by using the Vistara test and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Vistara test.

93. Defendants have also induced infringement, and continue to induce infringement, of one or more claims of the '720 Patent under 35 U.S.C. § 271(b). Defendants actively, knowingly, and intentionally induced, and continue to actively, knowingly, and intentionally induce, infringement of the '720 Patent by selling or otherwise supplying the Vistara tests with the knowledge and intent that third-party laboratories will use the Vistara tests supplied by Defendants to infringe the '720 Patent; and with the knowledge and intent to encourage and facilitate third-party infringement through the dissemination of the Vistara tests and/or the creation and

dissemination of promotional and marketing materials, supporting materials, instructions, product manuals, and/or technical information related to the Vistara tests.

94. Defendants specifically intended and were aware that the ordinary and customary use of the Vistara tests would infringe the '720 Patent. For example, Defendants sell and provide the Vistara tests, which when used in their ordinary and customary manner intended and instructed by Defendants, infringe one or more claims of the '720 Patent, including at least exemplary claim 1. Defendants further provide product manuals and other instructional materials that cause third-party laboratories to operate the Vistara tests for their ordinary and customary use. Defendants' third-party laboratories have directly infringed the '720 Patent, including at least exemplary claim 1, through the normal and customary use of the Vistara tests. Defendants accordingly have induced and continue to induce Defendants' third-party laboratories to use the Vistara tests in their ordinary and customary way to infringe the '720 Patent, knowing, or at least being willfully blind to the fact, that such use constitutes infringement of the '720 Patent.

95. Defendants have contributed to the infringement by third parties, including Defendants' third-party laboratories, and continue to contribute to infringement by third parties, of one or more claims of the '720 Patent under 35 U.S.C. § 271(c), by making, selling and/or offering for sale in the United States, and/or importing into the United States, the Vistara tests, knowing that those products constitute a material part of the inventions of the '720 Patent, knowing that those products are especially made or adapted to infringe the '720 Patent, and knowing that those products are not staple articles of commerce suitable for substantial non-infringing use.

96. Defendants have had knowledge of and notice of the '720 Patent and their infringement since at least June 2015, as evidenced by communications between Ravgen and Defendants.

97. Defendants' infringement of the '720 Patent was, and continues to be, willful and deliberate since at least June 2015, when Defendants' representatives communicated Defendants' interest in acquiring or licensing the Ravgen patent portfolio, including the '720 Patent.

98. Ravgen has been and continues to be damaged by Defendants' infringement of the '720 Patent, and will suffer irreparable injury unless the infringement is enjoined by this Court.

99. Defendants' conduct in infringing the '720 Patent renders this case exceptional within the meaning of 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Ravgen prays for judgment as follows:

A. That Defendants have infringed each of the Patents-in-Suit;

B. That Defendants' infringement of each of the Patents-in-Suit has been willful;

C. That Ravgen be awarded all damages adequate to compensate it for Defendants' past infringement and any continuing or future infringement of the Patents-in-Suit up until the date such judgment is entered, including pre- and post-judgment interest, costs, and disbursements as justified under 35 U.S.C. § 284;

D. That any award of damages be enhanced under 35 U.S.C. § 284 as result of Defendants' willful infringement;

E. That this case by declared an exceptional case within the meaning of 35 U.S.C. § 285 and that Ravgen be awarded the attorney fees, costs, and expenses incurred in connection with this action;

F. That Ravgen be awarded either a permanent injunction, or, at least, a compulsory ongoing licensing fee; and

F. That Ravgen be awarded such other and further relief at law or equity as this Court deems just and proper.

DEMAND FOR JURY TRIAL

Plaintiff Ravgen hereby demands a trial by jury on all issues so triable.

Dated: June 1, 2020

Respectfully submitted,

/s/ Deron R. Dacus

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